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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/085,906	02/27/2002	Vincent Ling	GNN-5343CP2	5219

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EXAMINER	
SWITZER, JULIET CAROLINE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/085,906	LING ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *7-9,13 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-12 and further electing the sequence in the specification as SARA31 (SEQ ID NO: 352) for prosecution in the paper filed 9/5/03 is acknowledged.

2. In a telephone conversation with Hathaway Russell on 10/7/03 the restriction requirement was clarified so as to confirm that applicant intended to also identify polymorphic repeat SEQ ID NO: 354 and additional primer SEQ ID NO: 353 for prosecution with the method claims.

3. A further telephone conversation with Hathaway Russell on 12/9/03 clarified that the elected polymorphic repeat did not appear to be the hR1 sequence recited in claims 7, 8, and 9, and that pursuant to the election of pr SEQ ID NO: 354 these claims would be withdrawn from prosecution. Claims 7-9 and 13-14 are therefore withdrawn from prosecution.

4. Thus, claims 1-6 and 10-12 are under prosecution, and claims which recite particular PMR sequences have been examined only insofar as they recite the elected PMR sequence and associated primers (SEQ ID NO: 352-354).

Sequence Rules Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): Figure 4A recites sequences that are no identified by proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, as needed, a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Drawings

6. The drawings are objected to because figure 4A is not in compliance with the sequence rules (as noted previously). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-6 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Claims

The claims are drawn to a method for determining the predisposition of a human subject to develop autoimmune disease via the detection of at least one polymorphic microsatellite

repeat (PMR) in the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence. The nature of the claimed invention is such that the practice of the invention is dependent on the knowledge of a relationship between PMR alleles and particular diseases or all autoimmune diseases. With regard to claims 10-12, these claims are drawn to detecting the variant or subtype of a PMR present in an individual.

Breadth of the Claims

Claims 1-3 and 5-6 are broadly drawn to the determination of a predisposition to any possible autoimmune disease, a disease classification which includes a wide variety of diseases of varying effects and etiologies. This is exemplified in claim 4 which recites a listing of some possible autoimmune diseases, including insulin-dependent diabetes mellitus, lupus, leprosy, and rheumatoid arthritis.

Further, claims 1 and 10 are broadly drawn to include detecting any polymorphic microsattelite repeat (PMR) within the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence. With regard to the detected PMR, claims 2, 3, 4, 5, 6, 11, and 12 are limited to the elected PMR sequence which is within the CTLA-4 gene (p. 12 of the spec).

The scope of all of the rejected claims specifically exclude the use of an "hR2 sequence" within the claimed methods. As noted in the 112 2nd rejection herein, the scope of this exclusion is unclear. The prior art is silent with respect to any sequence in the CTLA4 gene that is called the hR2 sequence. With regard to hR2, the specification teaches that IDDM, Grave's disease and hypothyroidism have been found to be associated with "certain alleles of the hR2 region of human CTLA-4 (p. 13), and that the PMR associated with the hR2 region of CTLA4 has the

sequence SEQ ID NO: 546, a 50 base pair sequence which has within it repeat consisting of 20 "AT" units p. 13-14). The parent application from which the instant application depends, 09/534061, which has been incorporated by reference, teaches that the hR2 repeat sequence is also referred to as the CTLA4 3' UTR microsatellite repeat (p. 15 of parent application). The prior art repeatedly refers to an (AT)n repeat polymorhism in the 3'UTR of the CTLA-4 gene (for example Yanagawa *et al.*, as cited in IDS and parent application) that has been shown to be associated with Graves' disease, IDDM, and hypothyroidism (Yanagawa *et al.*, Kotsa *et al.* and Marron *et al.*, all cited in the IDS). Thus, within the human costimulatory receptor locus a polymorphism in the CTLA-4 gene has been shown to be associated with at least these autoimmune diseases, but this polymorphic repeat is excluded from the scope of the instant claims.

Guidance in the Specification and Working Examples

The specification defines the costimulatory receptor locus as including the genetic region comprising the genes encoding the costimulatory receptors CD28, CTLA4 and ICOS, a region that is approximately 300 kb on chromosome 2q33. The specification provides 122 examples of PMR sequences within this region, each identified with a particular sequence identifier, and primers are given for the amplification of the sequences. The specification teaches that the elected sequence (SEQ ID NO: 354) is a PMR that is located within the CTLA4 gene (p. 12).

Furthermore, while it is noted that applicant's provide 122 putative PMR sequences that are "within the human costimulatory receptor locus" the claims encompass the use of any PMR sequence within this locus. The specification does not define any clear ends of the locus, and thus the scope of the claims encompasses the use of PMR sequences that are upstream or

downstream of the 318 kb that applicant screened, considering the possible breadth of the term "locus." These sequences are undisclosed and unpredictable. Furthermore many of the claims encompass the screening of putative polymorphic sequences which have not been demonstrated as displaying polymorphic alleles, as exemplified in example 5 where only 4 out of 25 of the tested PMR sequences demonstrated more than one allele. In order to utilize even the disclosed polymorphic sequences within the broadly claimed invention, one would have to first determine allelic variation within the PMR, which may or may not exist as these have not been screened within populations to demonstrate that the sequences referred to by applicant as PMR are in fact polymorphic within any or all human populations.

With regard to claims 10-12 which recite determining the polymorphic variant or subtype of a PMR sequence, with claims 11 and 12 being limited to the particular sequence, while one even if one could actually practice the method steps of the claimed invention (particularly with regard to claims 11 and 12), one would not know how to use the claimed invention. That is, absent some disclosure of a relationship between the detected PMR with a disease, condition or phenotype, it would be highly unpredictable how to utilize the claimed invention, beyond as a tool to study the markers themselves.

The specification prophetically states at page 14 that "The novel polymorphic markers described herein provide additional markers that may be more closely linked with certain autoimmune disorders or conditions." However, beyond such prophetic statements, the specification does not provide any guidance concerning which alleles of which polymorphisms are associated with which autoimmune disorders or conditions. Likewise, with regard to the elected SEQ ID NO: 354 no such guidance or disclosure is provided.

Example 1 of the specification (beginning on p. 56) describes the mapping, sequencing and assembly of 2q33 section of human chromosome 2. Described is the isolation of 6 BAC clones which were end sequenced and compiled into a hypothetical map, and compared with known GenBank sequences to order. The resulting map describes an approximately 381 kb sequence which is diagrammed in Figure 1, and referred to in the specification as the costimulatory receptor locus. Example 2 of the specification (p. 57) further discusses the features of this region and teaches that 20 potential coding sequences were identified within the region. Example 3 teaches the prediction of open reading frames using reading frame prediction programs. Example 4 (p. 59) discusses genomic microarray expression analysis to detect differentially transcribed genes within the genomic region in response to differentially treated CD4+ T cells. Clones which correspond to CTLA4 and ICOS non-transcribed regions were detected. Example 5 teaches that twenty five of the PMR sequences of the instant invention were tested for allelic polymorphism, and of these only four demonstrated polymorphisms, one of which was instant SEQ ID NO: 354 (SARA 31). Example 6 compares human ICOS to murine ICOS.

Level of Unpredictability and State of the Prior Art

The specification and the prior art provide no guidance as to which of the instantly disclosed polymorphisms are associated with which autoimmune diseases. The claims provide a list of autoimmune diseases that the instant methods can be used for determining a predisposition to, however, neither the specification nor the claims provide any guidance as to which PMR sequences are associated with which diseases. The association of a PMR sequence with a disease is highly unpredictable. There is no a priori way to predict if a given PMR sequence will

be associated with any autoimmune disease at all, let alone which specific diseases, a problem which is complicated by the fact that the specification has provided no guidance as to which alleles of the instant PMR sequences are in fact indicators of a predisposition for disease and which do not indicate a predisposition for disease. The prior art does not provide any guidance as to an association between any of these PMR sequences and autoimmune disease, nor does the prior art teach that all of the recited diseases are so associated that a single marker or set of markers could be used to indicate a predisposition to then all. Instead, the prior art teaches that in some cases even studies which examine linkage between genes and particular autoimmune diseases result in conflicting findings. Barbesino *et al.* (as cited in IDS) teach that "Discrepancies between studies may be explained by genetic differences between populations and/or by the use of different polymorphisms for the same genes (p. 1580)," thus supporting the assertion that it is highly unpredictable which PMR sequences may be associated with which autoimmmune diseases, if in fact any associations exist at all. Barton *et al.* (IDS) did not find an association between a polymorphic allele and rheumatoid arthritis. Furthermore, the prior art is replete with examples of a marker being associated with a disease in a single population but not in other test populations. For example, Shai *et al.* (1999, Human Molecular Genetics, Vol. 8, No. 4, p. 639-644) teach that a marker on human chromosome 1 is associated with Mexican American families with SLE but not in families with Caucasian ethnicity. Further, even if a particular marker is associated with one autoimmune disease in a population, it is highly unpredictable as to whether or not it will be associated with a different autoimmune disease. For example, Hatta *et al.* (1999, Genes and Immunity, Vol. 1, p. 53-60) teach an association of FcγRIIIb polymorphism with SLE in a population of Japanese patients, but no association was

observed between the same polymorphism and rheumatoid arthritis. Finally, if polymorphisms that are indicative of autoimmune disorder are located in one species of organism, it is highly unpredictable as to whether the same relationship would exist for different host organism. When discussing the mouse as a model for human SLE, Moser *et al.* (1998, PNAS USA, Vol. 95, p. 14869-14874) teach that generically in the search for disease genes causative of SLE, "Whether or not both species share any of the same susceptibility genes for lupus can only be known after the genes are identified (p. 14873)."

Quantity of Experimentation

The quantity of experimentation necessary to determine an association between any single autoimmune disease and a PMR is also quite high, requiring the screening of hundreds of patients from different populations in order to confirm the existence of a predictive association. Indeed, Epplen *et al.* (Electrophoresis, 1997, IDS) report that "Increasingly larger panels have to be screened for many different genetic markers in order to arrive at conclusions that stand the necessary statistical tests (p. 1582)." Furthermore, in the instant case, many of the claims encompass the screening of putative polymorphic sequences which have not been demonstrated as displaying polymorphic alleles, as exemplified in example 5 where only 4 out of 25 of the tested PMR sequences demonstrated more than one allele. In order to utilize even the disclosed polymorphic sequences within the broadly claimed invention, one would have to first determine allelic variation within the PMR, then one would have to determine association with disease, which association is highly unpredictable.

Conclusion

Thus, the instant claims are quite broad with regard to the autoimmune disease whose predisposition is being determined and with regard to which PMR sequences are associated with diseases and further with regard to the PMR sequences themselves. The prior art does not provide any clear guidance to lead the practitioner in choosing the appropriate PMR-autoimmune disease combinations. The level of unpredictability is extremely high with regard to the determination of an association between any autoimmune disease and any PMR. The specification does not provide any working examples which demonstrate that the instant PMR sequences are associated with autoimmune diseases,. Finally the quantity of experimentation required to reasonably confirm the association between any single PMR and any single autoimmune disease is quite high, and the quantity of experimentation required to confirm an association between ever PMR in the human costimulatory receptor locus and every autoimmune disease is even higher. For all of these reasons, it is concluded that undue experimentation is necessary to practice the claimed invention.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 3, 4, 5, 6, 10, 11, and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite over the recitation "wherein the PMR sequence is not an hR2 sequence," as neither the specification nor the claims define what is "an hR2 sequence," or how to identify one. The prior art is silent with respect to any sequence in the human costimulatory receptor locus that is called the hR2 sequence. With regard to hR2, the specification teaches that IDDM, Grave's disease and hypothyroidism have been found to be associated with "certain alleles of the hR2 region of human CTLA-4 (p. 13)," and that the PMR associated with the hR2 region of CTLA4 has the sequence SEQ ID NO: 546, a 50 base pair sequence which has within it repeat consisting of 20 "AT" units (p. 13-14). The parent application, 09/534061, which has been incorporated by reference, teaches that the hR2 repeat sequence is also referred to as the CTLA4 3' UTR microsatellite repeat (p. 15 of parent application). However, none of these teachings in the specification define an hR2 sequence. It is not clear if "an hR2 seqeunce" as recited in the claims is the same as the hR2 repeat sequence, or if it is a portion of the hR2 repeat sequence or if it is any repeat sequence that has an (AT)n repeat. It is not clear if an hR2 sequence must comprise instant SEQ ID NO: 546, or does the sequence include other alleles, does it minimally have to contain SEQ ID NO: 546 but could contain additional flanking sequence, etc? Instant SEQ ID NO: 546 is largely an "AT" repeat, and it is not clear if an "hR2" sequence is any AT repeat, for example. Furthermore, it is unclear from the specification and the claims if the "hR2" sequence must be a portion of the CTLA-4 gene, or if such sequences also are in other portions of the human costimulatory receptor locus. Given this lack of definition and the use of the arbitrary term hR2 sequence, the claims are indefinite.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Weber (US 5582979).

Weber teaches a method for determining the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject, said method comprising detecting at least one polymorphic microsatellite repeat in the human costimulatory receptor gene locus, wherein the PMR sequence is not an hR2 sequence to thereby determine the polymorphic variant or subtype of a PMR sequence in the costimulatory receptor locus in a human subject.

Specifically, Weber teaches a dinucleotide repeat polymorphism Mfd36 that is within the D2S72 locus and a method for detecting this repeat (Col. 30, Table 23, note reaction conditions in "OTHER COMMENTS" section). The instant specification teaches that the D2S72 locus is within the human costimulatory receptor locus (see p. 57, line 29). Thus, the teachings provided by Weber meet the limitations of the instant claim.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

Please note that beginning January 13, 2003 the examiner's telephone number will change to (571) 272-0753.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (703) 308-1119. Beginning January 13, 2003 Gary Benzion's telephone number will change to (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

December 12, 2003